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09/126,096	07/30/1998	EUGENE D. THORSETT	002010-137	8518

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EXAMINER

RAO, DEEPAK R

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 12/30/2003

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 35

Application Number: 09/126,096

Filing Date: July 30, 1998

Appellant(s): Thorsett et al.

Gerald F. Swiss

For Appellant

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EXAMINER'S ANSWER

This is in response to the appeal brief filed October 6, 2003.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

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(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-19 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

6,492,421

Thorsett et al.

12-2002

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-4, 6-7, 10 and 12-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 6,492,421. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no patentable distinction. The reference teaches compounds of structural formula I (see col. 105) wherein R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ form a heterocyclic ring, for example thiazolidinyl, pyrrolidinyl,

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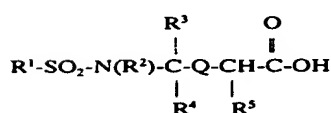
etc., which can be optionally substituted, e.g., with methyl (see col. 16, lines 13-44). Further, the reference teaches species that fall within the above genus, see the compounds of claim 10, e.g., the compound in col. 115, lines 19-20. The reference compounds are taught to be useful as pharmaceutical therapeutic agents for the treatment of diseases mediated by VLA-4, see claims 22-35. The instantly claimed compounds specifically require a substituent R^4 which is attached to the same carbon atom as R^3 , which substituent R^4 can be methyl. Therefore, the instantly claimed compounds are homologs of the reference disclosed compounds because they differ by addition of a methyl substituent (or addition of a $-CH_2$ group). One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds would be expected to possess similar properties and therefore, the same use as taught for the genus of the reference compounds.

(11) *Response to Argument*

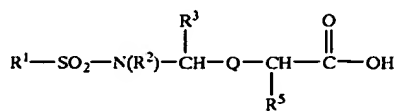
Appellants argue that a *prima facie* case of obviousness is not set forth. However, it has been clearly set forth that the instantly claimed compounds differ from the reference claimed compounds by having a substituent R^4 (which can be methyl) in place of the 'H' of the reference claims. The two structural formulae are depicted below for convenience:

S.No. 09/126,096

U.S. Patent No. 6,492,421



I



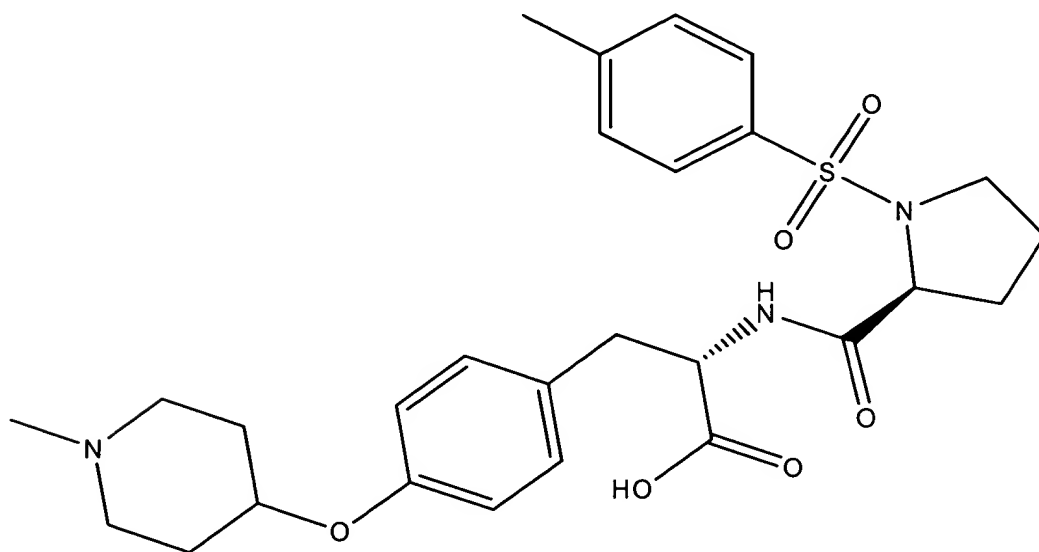
I

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Further, the reference teaches specific compounds of the above genus, see US 6,492,421 claim

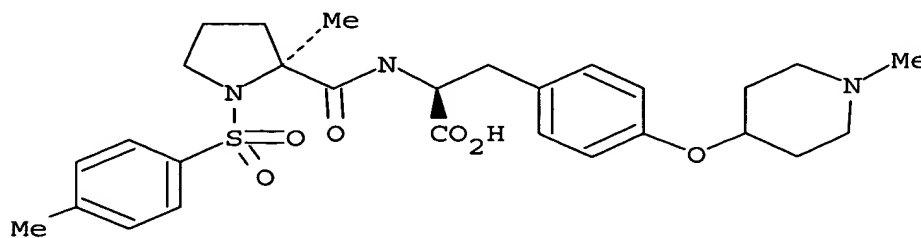
10, col. 115, lines 19-20 (the structural formula depicted below for convenience):

N-(toluene-4-sulfonyl)-L-prolyl-4-(1-methylpiperidin-4-oxy)-D,L-phenylalanine



The species falling within the instant claims of S.No. 09/126,026 drawn to formula I wherein R⁴ is methyl (e.g., claim 22, compound 5) is represented below:

N-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine



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Thus, as can be seen from the above structural representation the instantly claimed compounds differ from the reference compounds by a methyl substituent on the pyrrolidine ring.

Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a *prima facie* case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Further, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Weichert*, 152 USPQ 249; *Ex parte Henkel*, 130 USPQ 474; *In re Jones*, 74 USPQ 152, 154; *Ex parte Fischer*, 96 USPQ 345; *In re Fauque*, 121 USPQ 425; *In re Druey*, 138 USPQ 39. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient to show obviousness. Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art

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compounds". For all the above reasons, it is maintained that a prima facie case of obviousness has been established in the instant case.

Appellants cite *In re Papesch* and argue that structural similarity alone does not dictate obviousness of chemical compounds. This is not found to be persuasive because appellant has not provided a showing of unexpected results for the claimed compounds as compared to the reference compounds.

Appellants cite *Ex parte Burtner* to support their argument that homology alone does not determine patentability. However, the cited case is not found to be on point because in *Burtner*, the homologous series was in the alcohol moiety of the esters. Unlike in the cited case, in the instant compounds, a CH₃ group is substituted on a ring carbon atom and therefore, the issue at contention is clearly distinct from the structural relationship of the cited case. The ordinary artisan needs to make only one structural change to the reference compounds to arrive at the instant compounds, i.e., substitute a methyl group in the place of hydrogen. "Where claimed compounds are so similar in structure to the prior art compounds, sufficient motivation exists to make the claimed compounds in the expectation that the compounds of structural similarities will have similar properties." See *In re Payne*, 203 USPQ 245 (CCPA 1979). The test of patentability of a compound that is a homologue of a prior art compound is whether the claimed compound possesses beneficial characteristics which are unexpected and unobvious. *Sterling Drug, Inc. v. Watson Comr. Pats.* 135 Fsupp 173, 108 USPQ 37 (DCDC 1955). "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because

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homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.” See *In re Deuel*, 51 F.3d 1558, 34 USPQ 2d 1210, 1214 (Fed. Cir. 1995).

Appellant’s arguments *In re Coes*, *In re Langer* and *In re Lalu* have been fully considered but they were not deemed to be persuasive. Appellant argues that “the mere fact that there is “homology” should not automatically be equated with *prima facie* obviousness”. However, contrary to appellant’s arguments, the *Coes* court ruled that “[A]djacent homologues of old substances are unpatentable as new compounds particularly where the homologues are not markedly superior to the old substances”. Thus, *Coes*, is a lengthening-of-chain type case and is clearly different from the facts of the instant case. Also, the *Langer* case is with respect to sterically hindered amines as opposed to unhindered amines, and thus, the facts are remote from the instant case. *Lalu* is not on point for the instant situation because the case scenario in *Lalu* was between claimed products vs. prior art disclosed intermediate compounds and therefore, it was concluded that ‘the prior art does not provide motivation to stop the reference synthesis to investigate the intermediate compounds with the expectation of arriving at the claimed products’. Contrary to *Lalu*, in the instant case the reference teaches α -substituted compounds and further, teaches that the compounds have pharmacological properties which is sufficient to one of ordinary skill in the art to prepare the α,α -disubstituted compounds that are homologues of the reference compounds (i.e., wherein the second substituent is a methyl group) with reasonable expectation of arriving at compounds having properties similar to that of reference compounds.

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Appellant's citation of *Ex parte Biel* and *Ex parte Goonewardene* have been fully considered, however, these are not on point in the instant case because in the cited case the structural difference was not similar to the instant case. For example, in *Biel*, the methylene group (-CH₂-) was between a piperidine ring and an ester function which is clearly not similar to the situation in the instant case.

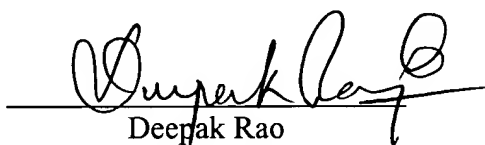
Appellant relies on Salgado et al., to rebut the prima facie case of obviousness, arguing that the reference shows superior properties for α,α -disubstituted compounds. First, the reference compounds are 2,2-dialkylcyclopropane carboxylic acids as compared to the instantly claimed nitrogen heterocycles, e.g., pyrrolidine and further, the properties discussed in the reference are 'resistance to hydrolysis' and 'enzyme cleavage process' with respect to plant growth regulators. Therefore, the reference does not provide a fair comparison of the claimed compounds with the reference compounds. Further, the reference statement regarding the enhanced property of the α,α -disubstituted compound was not stated in comparison of the α,α -disubstituted compound with the α -(mono)substituted compound. According to Salgado, 1-amino-2-substituted-cyclopropane-1-carboxylic acids are also effective and useful as plant growth regulators. Furthermore, it is well established that cyclopropane itself is a rigid molecule and shows chemical properties that are entirely different from other molecules including many of the members of cycloalkane family. This very rigidity of the cyclopropane may be contributing to the conformational restrictions discussed in the reference. Appellant's submission of the α,α -disubstituted cyclopropyl compounds exhibiting properties of plant growth regulators as evidence

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rebutting a prima facie case of obviousness of α,α -disubstituted pyrrolidine compounds useful as pharmaceuticals in itself is unsupported speculation.

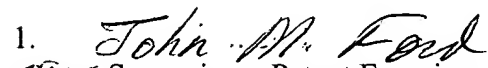
For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,


Deepak Rao
Primary Examiner
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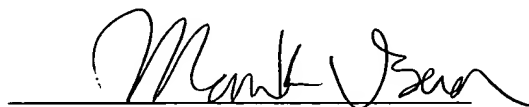
December 22, 2003

Conferees:

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Supervisory Patent Examiner
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2. Mark Berch
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